Cancer metastasis interfering vaccine

The present invention report describes a novel molecule that has been synthesized by a multivalent substrate and the idiotype parts of antibodies that recognize and bind antimetastatic peptides.

The molecule is used for the production by the living organism of antiidiotype antibodies [1-4] with antimetastatic properties.

The ability of cancer to metastasize is the most lethal characteristic of this disease [5], that remains mainly incurable and one of the most common causes of mortality in well developed countries[6].

Therefore the suppression and eradication of metastases is a major goal of alternative treatment strategies for cancer [6].

The ability of a cancer cell to metastasize depends by several properties, however high affinity binding with extracellular matrix molecules is currently considered as necessary. [7 8-12].

This ability is attributed to the enrichment of specific metastatic cell surface binding sites. These binding sites recognize specific aminoacid sequences situated on some extracellular matrix proteins such as laminin and fibronectin[13].

It has been reported that proteolytic fragments of laminin and fibronectin occupy metastatic cell surface binding sites and thus inhibit experimental metastasis [14]. The aminoacid sequences that are immediately related with this property have been discovered and described[10,15-29]. The sequence (peptide) YIGSR that recognizes a metastasis associated high affinity laminin receptor has been discovered on laminin [30] and the sequence RGDS, that recognizes a family of extracellular matrix receptors called integrins has been discovered on fibronectin [23-26,31-34 35,36].

It is presently well known that the metastatic ability of cancer cells can be experimentally inhibited if the binding sites described above are covered by the synthetic peptide YIGSR [37]. The same peptide has been also used for the in vitro selection of melanoma cell lines with high metastatic potential [38]. Moreover the radiolabeled peptides YIGSR and RGDS have been used in vivo for the detection of metastatic sites [28,29 39].

It was thus obvious since 1991 [40] that polypeptides which contain RGD and/or YIGSR sequences could provide a promising approach for the control and prevention of cancer metastasis.

However, despite of the above evidence, the peptides RGD or YIGSR, had no effect in the spontaneous metastasis model, and only multiple intravenous

administrations of polymers containing these sequences may result in a reduction of metastatic sites [40].

Several polymers containing these sequences have been proposed as antimetastatic agents in the past [35,40,41,41-58]. Unfortunately these efforts had minimum success because of the limited life span of these molecules in plasma [47,57,59-61].

The advantage of the present invention is that after vaccination with the molecule we describe, the immunological system is directed to produce specific antibodies with idiotype sequences that are similar to the antimetastatic peptides. Thus the living organism produces antibodies with properties comparable with the described peptide properties. As our pilot experiments indicated these antibodies offer significant defense against cancer metastasis.

During these experiments, serum derived from rabbits immunized with the peptide YIGSR has been used for the vaccination of mice, while other mice (controls) were immunized with non specific rabbit serum. After vaccination all mice were inoculated with the same amount of Lewis lung carcinoma cells 3LL. The mice were sacrificed after 20 days and the lungs were observed for the evidence of metastasis macroscopically and microscopically.

The immunized mice had significantly smaller tumors and less micrometastases around the lung vessels in comparison to controls. Macroscopically lung metastases were obvious only in control mice.

According to the present innovation for the preparation of the vaccine molecules of polylysine, polyethylenoglycol or any other polyvalent molecule can be used. On these molecules multiple Fab fragments or V regions (idiotypes) of gamma globulins (antibodies) are covalently attached. These parts have been prepared by polyclonal or monoclonal antibodies or by bio-engineering methods. The antibodies have been raised against the antimetastatic peptides YIGSR and/or RGD or other molecules containing these sequences. Thus novel polyvalent antigenic molecules are synthesized that can be used as antigens (vaccines). The multiple antigen recognition sequences (idiotypes) that are included in this molecule, have been raised against antimetastatic peptides YIGSR and/or RGD and for this reason have a shape complimentary to these peptides. Thus this molecule will lead the immune system to produce antiidiotype antibodies with a shape and properties that are analog to the original molecules (peptides).